

## Anxiolytics, Oral – Summary

September 2020

### FDA-APPROVED INDICATIONS AND DOSAGES<sup>1,2,3,4</sup>

Drug	Manufacturer	Indication(s)				Typical Dosage for Anxiety Disorder(s)*	Availability
		Anxiety Disorder	Panic Disorder	Other Anxiety Indication(s)	Other Indications		
alprazolam (Xanax®, Xanax XR)	generic, Pharmacia/ Pfizer	X (labeling states roughly corresponds to a diagnosis of GAD) (IR and ODT tablets; oral concentrate)	X (with or without agoraphobia)	Short-term relief of symptoms of anxiety (IR and ODT tablets; oral concentrate)	--	<i>Adults:</i> Initial dose (non-ER): 0.25 to 0.5 mg 3 times daily  Initial dose (ER): 0.5 mg to 1 mg once daily, preferably in the morning  Range: 0.75 to 4 mg/day; but doses up to 10 mg/day have been studied (ER range, 3 to 6 mg/day)	Tablet: 0.25 mg, 0.5 mg, 1 mg, and 2 mg  ODT tablet: 0.25 mg, 0.5 mg, 1 mg, and 2 mg (generic)  ER tablet: 0.5 mg, 1 mg, 2 mg, and 3 mg  Oral concentrate: 1 mg/mL <sup>†</sup>
buspirone HCl	generic	X (labeling states roughly corresponds to a diagnosis of GAD)	--	Short-term relief of symptoms of anxiety	--	<i>Adults:</i> Initial dose: 7.5 mg twice daily  Range: 15 to 30 mg/day in 2—3 divided doses (maximum: 60 mg/day)	Tablet: 5 mg, 7.5 mg, 10 mg, 15 mg, and 30 mg

GAD = generalized anxiety disorder; ER = extended release; IR = immediate release; ODT = orally disintegrating tablet

\* Dosing can vary based on type of anxiety disorder/anxiety symptoms; see Prescribing Information for full dosing details, including titration and tapering recommendations.

† Approved via an Abbreviated New Drug Application (ANDA) but marketed under the trade name Alprazolam Intensol™ by Roxane/West-Ward.

### FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)				Typical Dosage for Anxiety Disorder(s)*	Availability
		Anxiety Disorder	Panic Disorder	Other Anxiety Indication(s)	Other Indications		
chlordiazepoxide HCl	generic	X (subtype not specified)	--	Short-term relief of symptoms of anxiety; Preoperative apprehension/anxiety	Acute alcohol withdrawal	<i>Adults:</i> Initial dose: 5 to 10 mg 3 to 4 times daily  Range: 15 to 100 mg/day  <i>Pediatrics ≥ 6 years:</i> Initial dose: 5 mg 2 to 4 times daily  Range: 10 to 30 mg/day	Capsule: 5 mg, 10 mg, and 25 mg
clorazepate dipotassium (Tranxene T-Tab®)	generic, Recordati Rare Diseases	X (subtype not specified)	--	--	Acute alcohol withdrawal; Partial seizures (adjunctive therapy)	<i>Adults:</i> Initial dose: 30 mg/day, in divided doses or 15 mg as a single dose daily at bedtime  Range: 15 to 60 mg/day	Tablet: 3.75 mg (generic only), 7.5 mg, and 15 mg (generic only)
diazepam (Valium®)	generic, Roche	X (subtype not specified)	--	Short-term relief of symptoms of anxiety	Acute alcohol withdrawal; Muscle relaxant; Seizure disorders (adjunctive)	<i>Adults:</i> Initial dose: 2 mg 2 to 4 times/day Range: 2 to 10 mg 2 to 4 times daily  <i>Pediatrics ≥ 6 months:</i> Initial dose: 1 to 2.5 mg 3 to 4 times daily Range: individualized	Tablet: 2 mg, 5 mg, and 10 mg  Oral solution: 5 mg/5 mL  Oral concentrate: 5 mg/mL

GAD = generalized anxiety disorder; ER = extended release; IR = immediate release; ODT = orally disintegrating tablet

\* Dosing can vary based on type of anxiety disorder/anxiety symptoms; see Prescribing Information for full dosing details, including titration and tapering recommendations.

### FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)				Typical Dosage for Anxiety Disorder(s)*	Availability
		Anxiety Disorder	Panic Disorder	Other Anxiety Indication(s)	Other Indications		
lorazepam (Ativan®)	generic, Valeant/Bausch	X (subtype not specified)	--	Short-term relief of symptoms of anxiety; Insomnia due to anxiety/transient stress	--	<i>Adults and pediatric patients ≥ 12 years of age:</i> Initial dose: 1 mg 2 to 3 times daily  Range: 2 to 6 mg/day, largest dose prior to bedtime (maximum: 10 mg/day)	Tablet: 0.5 mg, 1 mg, and 2 mg  Oral concentrate: 2 mg/mL <sup>‡</sup>
meprobamate	Alembic	X (subtype not specified)	--	Short-term relief of symptoms of anxiety	--	<i>Adults:</i> Range: 1,200 mg to 1,600 mg/day, in 3 to 4 divided doses  <i>Children 6 to 12 years:</i> Range: 200 mg to 600 mg/day, in 2 to 3 divided doses	Tablet: 200 mg and 400 mg

GAD = generalized anxiety disorder; ER = extended release; IR = immediate release; ODT = orally disintegrating tablet

\* Dosing can vary based on type of anxiety disorder/anxiety symptoms; see Prescribing Information for full dosing details, including titration and tapering recommendations.

‡ Approved via an ANDA but marketed under the trade name Lorazepam Intensol by Roxane/West-Ward, in addition to other generic manufacturers.

### FDA-Approved Indications and Dosages (continued)

Drug	Manufacturer	Indication(s)				Typical Dosage for Anxiety Disorder(s)*	Availability
		Anxiety Disorder	Panic Disorder	Other Anxiety Indication(s)	Other Indications		
oxazepam	Actavis/Teva	X <sup>§</sup> (subtype not specified)	--	Short-term relief of symptoms of anxiety; Anxiety associated with depression	Acute alcohol withdrawal	<p><i>Adults and pediatric patients &gt; 12 years of age:</i> Initial dose: 10 to 15 mg 3 to 4 times daily</p> <p>Range: 10 to 30 mg 3 to 4 times daily</p> <p><i>Children 6 to 12 years:</i> Absolute dosage has not been established</p>	Capsule: 10 mg, 15 mg, and 30 mg

GAD = generalized anxiety disorder; ER = extended release; IR = immediate release; ODT = orally disintegrating tablet

\* Dosing can vary based on type of anxiety disorder/anxiety symptoms; see Prescribing Information for full dosing details, including titration and tapering recommendations.

‡ Approved via an ANDA but marketed under the trade name Lorazepam Intensol by Roxane/West-Ward, in addition to other generic manufacturers.

§ Labeling states that this product has been found to be particularly useful in the management of anxiety, tension, agitation, and irritability in older patients.

All of the agents listed in the above table are classified as Schedule IV controlled substances with the exception of buspirone, which is not a controlled substance.

While these medications may have other United States (US) Food and Drug Administration (FDA)-approved indications, this summary document will focus on their use as anxiolytics.

Diazepam is also available in rectal gel (not indicated for anxiety) and solution for injection formulations, and lorazepam is also available as a solution for injection; this review will focus on the oral formulations of these medications.

## OVERVIEW

Anxiety disorders are the most common of all the mental health disorders. Anxiety disorders include generalized anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder.<sup>5</sup> While post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) have historically been grouped under the broad classification of anxiety disorders, the newest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), DSM-5, considers PTSD under the classification of trauma- and stressor-related disorders and OCD under obsessive-compulsive and related disorders to further distinguish these from other anxiety disorders.<sup>6</sup> Additional disorders in this group are specific phobias and acute stress disorders.<sup>7</sup>

- GAD affects about 2.7% of the adult US population annually.<sup>8</sup>
  - ❑ 5.7% of adults in the US will experience GAD in their lifetime. Women are more likely than men to be affected by anxiety.
  - ❑ Characterized by pathological anxiety, which is excessive, chronic, and typically interferes with ability to function in normal daily activities.
- SAD affects approximately 7.1% of Americans each year.<sup>9</sup>
  - ❑ The most common anxiety disorder in the US; third most common psychiatric disorder after depression and alcohol abuse.
  - ❑ Characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur.
- Panic disorder is estimated to affect 2.7% of Americans per year.<sup>10</sup>
  - ❑ Considered a severe, chronic anxiety disorder.
  - ❑ Characterized by recurrent episodes of panic attacks and the development of fear or anxiety regarding the possibility of future panic attacks.
- OCD affects about 1.2% of the population in the US.<sup>11</sup>
  - ❑ Anxiety disorder that equally affects women and men.
  - ❑ Characterized by recurrent, unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions).
- PTSD affects 3.6% of the adult US population.<sup>12,13,14,15,16,17</sup>
  - ❑ Fourth most common psychiatric condition
  - ❑ Characterized by re-experiencing the trauma, emotional numbing, avoidance, and increased arousal.

Cognitive Behavior Therapy (CBT) and other variants of psychotherapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) to support their use either alone or in combination with pharmacotherapy.<sup>18,19</sup> Medications from the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) drug classes are generally the preferred chronic pharmacologic intervention for the treatment of anxiety disorders. The role of benzodiazepines is limited primarily to the short-term setting for acute symptoms or as short-term augmentation therapy to the SSRIs or SNRIs when treatment is initiated due to the delay in onset of SSRIs and SNRIs. Use of benzodiazepines is further limited in the pediatric patient population, as these agents have not been found to be effective. It may be reasonable to consider their use in pediatric patients for a very short

period of time as an adjunctive therapy in patients with severe anxiety. In general, benzodiazepines should not be used as needed, as this can lead to symptom relief followed by worsening symptoms due to inconsistent drug exposure.<sup>20</sup>

Benzodiazepines exert their effects in the central nervous system (CNS) and can produce various levels of CNS depression ranging from skeletal muscle relaxation and sedation to anticonvulsant effects.<sup>21</sup> These agents act at the gamma-aminobutyric acid (GABA)-benzodiazepine receptor of which the GABA-A receptor is the main receptor subtype in the CNS, and thereby the primary location for benzodiazepines to exert their effects. There are 3 primary types of benzodiazepine receptors (BNZs) that are coupled to the GABA-A receptors. Depending on the receptor location and receptor targeted, these agents have various inhibitory effects. The BNZ1 receptor is found in the CNS and is thought to be involved in sleep. The BNZ2 receptor is located in the cerebral cortex and spinal cord and is involved in muscle relaxation, anticonvulsant effects, motor coordination, and memory. The third benzodiazepine receptor, BNZ3, is found in the peripheral tissues.

Benzodiazepines exert their pharmacological activity through nonspecific binding to the BNZ1 and BNZ2 receptors which potentiates the effects of the inhibitory neurotransmitter GABA.<sup>22</sup> The onset and duration of activity of a benzodiazepine is influenced by whether the medication has active metabolites as well as by the 2-compartment pharmacokinetic model of distribution.

Alprazolam has a rapid onset of action with a short duration and minimally active metabolites.<sup>23</sup> Chlordiazepoxide and clorazepate have an intermediate onset of action with a long duration of action and active metabolites. Diazepam has a rapid onset and a long duration with active metabolites. Lorazepam has a rapid onset of action and intermediate duration with inactive metabolites. Oxazepam has a slow onset with an intermediate duration and inactive metabolites.

Buspirone and meprobamate are considered to be non-benzodiazepine anxiolytics.<sup>24</sup> Buspirone is structurally different from other anxiolytics and does not have anticonvulsant effects, impede psychomotor abilities, or have the potential for physical dependence. Due to these pharmacological differences, buspirone generally does not result in sedation or have an effect on alertness. Although the exact mechanism of action of buspirone is not well understood, it exhibits high affinity at certain serotonin receptors (5-HT<sub>1A</sub> and 5-HT<sub>2</sub>) and moderate activity at the D<sub>2</sub> dopamine receptor.<sup>25</sup> Its effects in anxiety likely may be related to activity on more than one neuropathway, as it inhibits serotonergic activity but increases noradrenergic and dopaminergic activity.<sup>26</sup> Overall, the primary activity of buspirone has been determined to be mixed agonism/antagonist at the 5-HT<sub>1A</sub> receptor. It is indicated for the treatment of GAD as well as for the short-term relief of anxiety symptoms and alleviates autonomic and motor symptoms of anxiety. Like SSRIs and SNRIs, the onset of its action can be delayed (up to 2 weeks) following chronic administration; thus, it is not utilized for the acute treatment of anxiety.

Meprobamate is also distinct from the other anxiolytics as it is similar in structure to the skeletal muscle relaxant carisoprodol.<sup>27</sup> Like buspirone, the exact mechanism of action for meprobamate is not well understood but likely is mediated through depressive effects within the CNS. It carries the potential for physical and psychological dependence as well as for abuse. In addition, an overdose can lead to respiratory depression and coma. Although it is indicated for the treatment of anxiety disorders and short-term symptom relief from anxiety in adults and children 6 years and older, it is generally not utilized for these purposes, as alternative medications provide improved safety profiles. Since its role in the modern treatment of anxiety disorders is limited, details on this agent in this review are limited.

The 2012 World Federation of Societies of Biological Psychiatry (WFSBP) guidelines recommend SSRIs, SNRIs, and pregabalin as first-line therapies for the treatment of anxiety, obsessive-compulsive, and post-traumatic stress disorders in primary care.<sup>28,29</sup> Tricyclic antidepressants (TCAs) are equally effective for some disorders, but many are less well tolerated than SSRIs and SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. In general, the anxiolytic effects of benzodiazepines begin minutes after administration, but these agents carry the potential for dependence following a few weeks or months of continuous use. However, these agents can be useful during the first weeks of treatment initiation for serotonin regulating medications to minimize anxiety. They should be dosed on a consistent schedule and only used as needed in certain circumstances. Although these guidelines focus on medications, non-pharmacological interventions were also considered. CBT and other variants of behavior therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) to support their use either alone or in combination with the above medications.

## **Generalized Anxiety Disorder (GAD)**

The Anxiety and Depression Association of America (ADAA) released a Clinical Practice Review on GAD in July 2015.<sup>30</sup> First-line and second-line treatments include psychotherapy or pharmacotherapy. For both adults and children, SSRIs or SNRIs are considered first-line pharmacotherapy. For second-line pharmacotherapy, benzodiazepines (diazepam, alprazolam, lorazepam, clonazepam) or buspirone are recommended for adults, whereas venlafaxine XR is recommended for pediatric patients 6 to 17 years of age. Other medications that can be considered for adults include hydroxyzine, imipramine, trazodone, mirtazapine, bupropion XL, pregabalin, quetiapine, and vortioxetine. For children, diazepam and hydroxyzine are listed as potential third-line therapies. Potential pharmacological augmentation agents for use in adults include olanzapine, risperidone, quetiapine, and pregabalin.

The American Academy of Family Physicians (AAFP) published a review article on the diagnosis and management of generalized anxiety disorder and panic disorder in adults in May 2015.<sup>31</sup> Psychotherapy has been found to be as effective as pharmacotherapy for GAD, with cognitive behavior therapy (CBT) demonstrating the highest level of evidence (Evidence Rating: A). For GAD, SSRIs (e.g., escitalopram, fluoxetine, paroxetine, sertraline) are considered first-line (Evidence Rating: B). The SNRIs duloxetine and extended-release venlafaxine, as well as buspirone, are considered to be other first-line agents for GAD. Second-line agents include TCAs (amitriptyline, imipramine, and nortriptyline), pregabalin, quetiapine, and hydroxyzine. MAOIs are considered third-line therapy. Treatment should be individualized and may require a combination of interventions (Evidence Rating: C). Benzodiazepines (e.g., diazepam, lorazepam) may be useful as augmentation during acute treatment; however, dependence and tolerance impede the long-term use of these agents in this setting.<sup>32</sup> As tolerance can develop to the effects of benzodiazepines, short-term use is only recommended during acute episodes; although these agents may alleviate anxiety symptoms when used in combination with antidepressants, they do not result in improved long-term outcomes (Evidence Rating: B). These agents should generally only be used for the short-term acute management of uncontrolled anxiety with slow tapering to prevent symptom recurrence. Benzodiazepines with short half-lives (e.g., alprazolam) are usually not preferred due to the increased likelihood for adverse events as well as addiction.



The International Consensus Group on Depression and Anxiety (ICGDA) recommends SSRIs, SNRIs (venlafaxine), non-sedating TCAs, buspirone, or hydroxyzine as first-line treatments for GAD.<sup>33</sup> CBT is a nonpharmacological treatment option for these patients as well.

Specific to GAD, the WFSBP guidelines recommend first-line treatment with SSRIs, SNRIs, or pregabalin.<sup>34</sup> Buspirone and the antihistamine hydroxyzine are considered to be other options; however, hydroxyzine use should be reserved for patients who have had inadequate relief or intolerance to other therapies due to its sedating properties. CBT is another treatment modality recommended in the WFSBP guidelines for these patients. Long-term treatment with benzodiazepines should be reserved for patients who have failed CBT and other medication options.

## **Social Anxiety Disorder (SAD)**

The ICGDA expert panel guidelines recommend SSRIs as first-line therapy for chronic SAD with trial of another SSRI prior to trial of other agents.<sup>35</sup> The benzodiazepine clonazepam is considered to be a disorder-specific treatment option for these patients, but it is only FDA-approved for various seizure disorders and panic disorder.<sup>36,37</sup>

According to the WFSBP guidelines, SSRIs and venlafaxine are recommended first-line therapies for chronic SAD. TCAs have not been found to be effective in these patients, and there is minimal evidence to support the use of benzodiazepines for these patients. Exposure therapy and CBT are nonpharmacological options for this chronic disorder. In patients unresponsive to other treatment modalities, the MAOI phenelzine may be considered.<sup>38</sup>

## **Panic Disorder (PD)**

The 2009 American Psychiatric Association (APA) legacy treatment guidelines recommend SSRIs, SNRIs, TCAs, and benzodiazepines as first-line pharmacotherapy for panic disorder. The guideline further states that all are roughly comparable in efficacy, but the relatively favorable safety and side effect profile of SSRIs and SNRIs make them the best initial choice for many patients.<sup>39</sup> SSRIs have the largest evidence base for the condition. Benzodiazepines are appropriate as monotherapy only in the absence of a co-occurring mood disorder and may be useful as adjunct to antidepressants to treat residual anxiety symptoms.

The ICGDA guidelines also state that benzodiazepines may be required during the initial phase of treatment for panic disorder.<sup>40</sup> The WFSBP guidelines state that short-acting benzodiazepines may be required for severe attacks in panic disorder patients, but that SSRIs and venlafaxine are considered first-line treatments for these patients.<sup>41</sup>

## **Obsessive-Compulsive Disorder (OCD)**

The 2007 APA legacy treatment guidelines on OCD recommend SSRIs as the first medication trial for OCD with choice of agent based on the potential side effect profile.<sup>42</sup> The TCA clomipramine is also a recommended pharmacological treatment option for these patients. Buspirone is listed as a potential augmenting agent following trial and failure of other first- and second-line treatments, as there is less evidence to support its use for this purpose. Use of benzodiazepines as monotherapy for OCD includes case reports for clonazepam and alprazolam. As a result of the limited evidence to support their efficacy, benzodiazepines are not recommended as monotherapy for these patients.



The WFSBP guidelines have a similar position as the APA and state that in general, benzodiazepines have not been found to be efficacious for the treatment of OCD; first-line therapies for these patients are SSRIs and the TCA clomipramine.<sup>43</sup>

## Post-Traumatic Stress Disorder (PTSD)

The 2004 APA legacy treatment guidelines on PTSD state that psychotherapy and pharmacotherapy are appropriate initial treatment modalities, with SSRIs being considered first-line pharmacological therapy.<sup>44</sup> Other antidepressants may also be helpful for these patients. Use of benzodiazepines is discussed as a potential treatment strategy due to their ability to decrease anxiety and improve sleep; however, these have not demonstrated efficacy for treating the primary symptoms of PTSD and carry the potential for addiction and rebound of symptoms upon discontinuation. As a result, monotherapy with benzodiazepines is not recommended. At the time of guideline publication, there was inadequate evidence to recommend the use of buspirone for PTSD.

According to the WFSBP, long-term treatment is required for patients with PTSD, and first-line therapy includes SSRIs or venlafaxine. Efficacy for long-term use of the SSRIs fluoxetine and sertraline and the SNRI venlafaxine has been demonstrated.<sup>45</sup> The ICGDA also recommends first-line treatment with an SSRI or with trial of another SSRI prior to other therapies. TCAs and mood stabilizers have also been proposed as disorder-specific treatment for these patients.<sup>46</sup>

## SPECIAL USAGE CONSIDERATIONS<sup>47,48,49,50,51,52,53</sup>

Benzodiazepines carry a Boxed Warning regarding concurrent use with opioids and the potential for profound sedation, respiratory depression, coma, and death. As a result, concurrent use of these medications should only occur in patients who do not have sufficient alternatives. Use the lowest dose as well as the shortest duration of concurrent therapy in order to minimize these potential risks. Patients should be monitored for respiratory depression and sedation if these medications are used concurrently. In September 2020, the FDA released a Drug Safety Communication and MedWatch regarding class-wide safety labeling changes for the benzodiazepines to ensure their safe use. The FDA is requiring an update to the Boxed Warning for these products to include the potential for abuse, misuse, addiction, physical dependence, and withdrawal reactions. Buspirone does not carry a Boxed Warning.

Benzodiazepines are contraindicated in patients with known hypersensitivity to a benzodiazepine or components of the formulation. Acute narrow-angle glaucoma is a contraindication to use of alprazolam, clorazepate, diazepam, and lorazepam, and open-angle glaucoma is a contraindication to use of diazepam. Oral diazepam is also contraindicated in patients with liver disease, patients < 6 months of age, patients with myasthenia gravis, and in patients with sleep apnea or severe respiratory impairment. Alprazolam is contraindicated in combination with CYP3A inhibitors. Oxazepam is contraindicated in the treatment of psychoses.

Buspirone is contraindicated in patients with a hypersensitivity to the agent. Buspirone is also contraindicated in combination or within 14 days of discontinuation of a monoamine oxidase inhibitor (MAOI) due to the potential for serotonin syndrome.

Safety concerns occurring with benzodiazepines include dose-dependent respiratory depression, physiological dependence, the potential for withdrawal symptoms, and neuropsychiatric adverse effects. These medications also have the potential to increase the likelihood for falls in elderly patients by up to 50%. When used concurrently with another CNS depressant, respiratory depression can be

fatal. Although the risk for benzodiazepine dependence is highest with increased dosages and extended periods of treatment, it can occur at usual doses within 3 to 6 weeks of treatment. To minimize the potential for withdrawal symptoms, benzodiazepines, particularly agents with a short half-life, should be tapered slowly. Potential neuropsychiatric adverse effects (e.g., amnesia, fatigue, somnolence, impaired coordination, changes in executive function) can occur with benzodiazepines, limiting their use for extended periods of time for the treatment of anxiety. Other potential adverse effects of benzodiazepines include drowsiness, dizziness, appetite stimulation, impaired cognition, and changes in weight.

Potential adverse reactions of buspirone include dizziness, drowsiness, headache, nervousness, and nausea. Warnings and precautions for buspirone include akathisia or restlessness, CNS depression, and serotonin syndrome if given concurrently with other serotonergic agents, as described above. Due to buspirone's dopamine receptor antagonism, patients should be monitored for movement disorders (e.g., akathisia, dystonia). Patients should use caution if driving or operating machinery due to the potential for CNS depression. If concurrent use with another serotonergic agent or an MAOI is required, patients should be monitored for mental status changes, blood pressure increases, neuromuscular changes, gastrointestinal symptoms, and seizures.

All of the anxiolytic benzodiazepines require dose adjustments in hepatic impairment, with the exception of oxazepam. Chlordiazepoxide, diazepam, and lorazepam require dose adjustments in renal impairment. Buspirone should be used cautiously in mild to moderate hepatic impairment with low initial dosing due to increased drug levels and an extended half-life. Use of buspirone should be avoided in patients with severe hepatic impairment. In patients with a creatinine clearance (CrCl) > 70 mL/min, no dosage adjustments for buspirone are recommended. For patients with a CrCl of 11 to 70 mL/min, the dosage should be adjusted based on the amount of renal insufficiency; however, specific dosage adjustments are not recommended. In patients with severe renal impairment (CrCl < 10 mL/min), buspirone should not be used.

Use of a benzodiazepine is not recommended during pregnancy or in women who plan to become pregnant. In the first trimester, exposure to these agents can increase the likelihood for congenital malformation as well as other abnormalities, and in the third trimester, exposure can result in withdrawal symptoms in newborns. Benzodiazepines generally should not be used in this patient population, unless it is determined the benefits outweigh the risks. In general, the use of benzodiazepines in pediatric patients in the outpatient setting for anxiety is not well established, and use for this purpose is not recommended.

Benzodiazepines are susceptible to drug interactions with other medications that inhibit or induce the cytochrome p450 (CYP450) enzymes, especially agents affecting CYP3A4 or CYP2C19. As a result, increased monitoring, as well as dose adjustments, may be necessary. Concurrent use of benzodiazepines with other medications that cause CNS depression can lead to additive effects; caution should be exercised if these medications are used concomitantly. As diazepam is metabolized by CYP3A4 and grapefruit juice is a potent CYP3A4 inhibitor, grapefruit juice should be avoided during diazepam therapy. The effects of oral contraceptives on the levels of benzodiazepines vary based on the metabolism of the benzodiazepine.

Well-controlled studies with buspirone in pregnancy have not been conducted; however, adverse effects have not occurred in animal studies. Buspirone is not FDA-approved for the treatment of GAD in pediatric patients as data from placebo-controlled studies did not demonstrate a significant difference

compared to placebo. Buspirone should be administered consistently with or without food. Large amounts of grapefruit juice should be avoided while receiving buspirone therapy.

The 2019 American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends avoiding short-, intermediate-, and long-acting benzodiazepines in older adults due to an increased sensitivity to these agents as well as the increased potential for cognitive impairment, delirium, falls, fractures, and motor vehicle accidents (strength of recommendation: strong, quality of evidence: moderate).<sup>54</sup> It is noted that these agents may be acceptable in older adults for seizure disorders, rapid eye movement sleep behavior disorder, ethanol or benzodiazepine withdrawal, periprocedural anesthesia, and for severe generalized anxiety disorder. The AGS also states that meprobamate should also be avoided in this population due to its sedating properties and high incidence of physical dependence (strength of recommendation: strong, quality of evidence: moderate). Use of buspirone in older adults is not included on the list of potentially inappropriate medications for older adults.

## PLACE IN THERAPY

All of the agents included in this review are FDA-approved for anxiety or specific subtypes of anxiety; other FDA-approved indications for benzodiazepines include alcohol withdrawal, insomnia, seizure disorders, and muscle spasms. In general, the oral anxiolytic agents included in this review, and the benzodiazepines in particular, are not appropriate for long-term use. Buspirone has a unique mechanism of action and is only FDA-approved for anxiety disorders or the short-term relief of anxiety symptoms. It does not carry the same safety concerns as benzodiazepines and is the only agent in this therapeutic class that is not a controlled substance. Meprobamate as well as benzodiazepines are schedule IV controlled substances.

Generally, SSRIs and SNRIs are treatment options for anxiety disorders but are limited initially by their delayed onset of effect. In contrast, the use of benzodiazepines is limited primarily to the short-term setting for acute symptoms or as short-term augmentation therapy to the SSRIs or SNRIs when treatment is initiated due to the delay in onset of SSRIs and SNRIs. As a result, these agents may be considered to be second- or third-line adjunctive therapies. Buspirone is generally used as a first- or second-line agent for generalized anxiety disorder, but it has a delay in onset of effects (up to 2 weeks). It is useful for the management of anxiety disorders or the short-term relief of the symptoms of anxiety due to its improved safety profile compared to benzodiazepines. Meprobamate is not used in modern practice for the treatment of anxiety due to its safety profile.

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